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Research Article

A Randomized, Open-Label, Two-way Crossover Bioequivalence Study of Cilacar Tablet Compared with Atelec Tablet in Healthy Volunteers Under Fasting Condition

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Abstract

Cilnidipine is a novel L/N type calcium channel blocker, approved in several countries world-wide for the treatment of hypertension and is also well-established for its varied pleiotropic benefits. Cilnidipine was first approved in India in 2007, for the treatment of mild to moderate hypertension and since then has been a widely trusted and prescribed molecule. We conducted an open label, analyst blind, randomized, two-treatment, two-period, two sequence, single dose, crossover study to assess and compare the bioequivalence of test product Cilacar 10 mg and 20 mg tablet with reference product Atelec® 10 mg and 20 mg tablet, respectively in healthy volunteers. Blood samples were collected pre-dose and at regular intervals post-dose up to 24 hours. Plasma drug levels were determined with a validated chromatographic method. Pharmacokinetic parameter (C_{max}), (AUC_{0-t}), ($AUC_{0-\infty}$), (T_{max}), ($T_{½}$) and (K_{el}) was calculated. The 90% confidence intervals on the mean of difference between Cilacar 10 mg and Atelec® 10 mg were 82.61% to 121.80%, 88.35% to 109.72%, and 87.54% to 110.52% and The 90% confidence intervals on the mean of difference between Cilacar 20 mg and Atelec® 20 mg were 89.65% to 116.08%, 88.09% to 111.30%, and 88.35% to 110.79% for C_{max}, AUC ($_{0-t}$) and AUC ($_{0-\infty}$) respectively. All the volunteers completed the study. It can be concluded from the results, the test product Cilacar 10 mg and 20 mg and the reference product Atelec® 10 mg and 20 mg tablet met the required bioequivalence criteria. Both products were safe and well tolerated.

Keywords Bioequivalence, Cilnidipine, Calcium channel blocker, Hypertension, and Blood pressure

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INTRODUCTION

Hypertension, a multifactorial and a multifaceted disease, poses a substantial public health burden on the cardiovascular health and healthcare systems of India. It is estimated to be the third leading cause of morbidity and mortality after household air-pollution and tobacco smoking. Hypertension is an independent and major risk factor for cardiovascular disease and is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India.[1,2]

In addition, hypertension progressively increases the severity of renal disease and is a strong predictor of end-stage renal disease.[3] Thus, since the past few years, anti-hypertensive treatments that offer end-organ protection benefits are gaining significant importance in research and practice. Several classes of antihypertensive agents have been in clinical use, including diuretics, α-blockers, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARB), and calcium channel blockers (CCBs) as well.[4]

Cilnidipine is a novel, and yet well-established CCB in the South-east Asian and some European countries for the management of essential hypertension. The L & N blocking CCB is known for its unique reno-protective and sympatholytic properties that distinguishes it from the other existing L-type CCBs, such as Amlodipine. Due to its unique mode of action, apart from its anti-hypertensive effects it also has 'pleiotropic benefits' such as improvement in renal function, reduction in heart rate, reduction in the morning BP, improvement in insulin sensitivity, improvement in left ventricular function, reduction in serum uric acid levels and improvement in pedal edema which is a concerning side effect seen with the conventional CCBs – all of these benefits documented with numerous trials across the globe.

In recent animal studies, Cilnidipine has been shown to reduce the size of cerebral infarction and may prevent severe consequences after a cerebrovascular attack. Cilnidipine mediates its neuro-protective effects by reducing oxidative stress, enhancing survival signals, and inhibiting death signals from Cytochrome C release, caspase 3 activation, and poly (ADP-Ribose) polymerase (PARP) cleavage.[5,6] Thus, the molecule is established as a reno-protective, cardio-protective, and neuro-protective CCB.

A recent meta-analysis concludes Cilnidipine to be the first-line CCB for the management of hypertension either as a monotherapy or as a combination therapy.[7] Cilnidipine is approved for use in Japan under the brand name, Atelec® by Ajinomoto Pharmaceuticals.

Cilnidipine is a BCS class 2 molecule, highly lipophilic, with very low solubility in water and due to its first pass metabolism, has low oral bioavailability (≅30%).[8] Thus, to enhance the dissolution and absorption of Cilnidipine, the brand Cilacar (Unique Pharmaceutical Laboratories, a division of J B Chemicals & Pharmaceuticals Ltd.), utilizes amorphous Cilnidipine combined with a Novel Insoluble Drug Absorption Technology (NIDAT)* and micronized particles of the active ingredient. With an objective to prove pharmacokinetic equivalence with the innovator brand Atelec®, we conducted two bioavailability and bioequivalence studies in healthy volunteers, comparing Cilacar (Test=T) (with NIDAT Technology) in comparison with Atelec® (Reference=R) for both the 10 and the 20 mg strengths of Cilnidipine.

MATERIAL AND METHODS

Two parallel studies were conducted separately one for 10 mg and the other for 20 mg with 24 and 32 healthy volunteers respectively, the details of which are described below.

Design

Each study was an open label, randomized, analyst blind, two-treatment, two-sequence, two-period, cross-over, single dose, bioequivalence study of the test product (Cilacar), and the reference product (Atelec®), in healthy, adult human subjects under fasting condition.

Objective

Pharmacokinetics: To compare the single dose oral bioequivalence of the test product, Cilacar 10 and 20 mg tablet (Cilnidipine tablet IP 10 mg and 20 mg) manufactured by Unique Pharmaceutical Laboratories (A Division of J. B. Chemicals & Pharmaceuticals Ltd.), India and Atelec® 10 and 20 mg tablet (Cilnidipine tablet 10 mg and 20 mg) manufactured by Ajinomoto Pharmaceuticals Co., Ltd., Japan in healthy, adult, human subjects under fasting condition.

Safety: To assess the safety of the Test and the Reference products.

Investigational Products

Test Formulation (T): Cilacar 10 mg and 20 mg tablet (Cilnidipine tablet 10 mg and 20 mg), Manufactured by Unique Pharmaceutical Laboratories (A Division of J.B. Chemicals & Pharmaceuticals Ltd.) India.

Reference Formulation (R): Atelec® 10 mg and 20 mg tablet (Cilnidipine tablet 10 mg and 20 mg), Manufactured by: Ajinomoto Pharmaceuticals Co., Ltd. Japan.

Number of Subjects

Twenty-four healthy human volunteers were recruited for the Cilacar 10 mg and 32 healthy human volunteers for the Cilacar 20 mg were recruited. The volunteers aged from 18 to 45 years, had a weight not less than 50 kg and a body mass index from ≥18.00 kg/m^2 and < 30.00 kg/m^2. Compliance with pre-defined inclusion and exclusion criteria was checked before the study started. Inclusion of subjects was based on demographic data, medical and surgical history, physical examination, vital signs, and clinical laboratory investigations. Information about the study was given in writing and orally, and all subjects participating in this trial signed the informed consent.

Ethical Considerations

This study was conducted ethically in accordance with the principles of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, 64th World Medical Association– General Assembly, Fortaleza, Brazil, October 2013), all other pertinent regulatory requirements of Schedule Y & its Amendments, CDSCO Guidelines for Bioavailability & Bioequivalence Studies, March 2005, Indian Council of Medical Research (Ethical Guidelines for Biomedical Research on Human Participants, 2017), New Drugs and Clinical Trial Rules, GSR 227 E dated 19/03/19, Guidance on GCP & GLP. The study did not commence until IEC approved the protocol with the corresponding ICFs. No subject was enrolled in the study without obtaining written informed consent and subjects were under medical supervision throughout their stay in the clinical facility to ensure safety and well-being of the subjects.

Study Procedures

Treatment Administered

A single oral dose of Test Product (T); One Cilacar 10 mg and 20 mg tablet (Cilnidipine Tablet IP 10 mg and 20 mg) or Reference Product (R); one Atelec® 10 mg and 20 mg tablet (Cilnidipine Tablet 10 mg and 20 mg) was administered at 0.00 hours of each period with 240 ml of water at ambient temperature in sitting posture as per the randomization schedule. Subjects received the alternate 'treatment' in the subsequent periods, in such a way that each subject received both the 'treatments' by the end of the study. There was a washout period of 7 days between two consecutive dosing and the housing of volunteers was 11.00 hours before dosing and until 24.00 hours post-dose.

Blood Sample Collection and Sample Processing

Serial blood samples were collected from each subject via an indwelling cannula placed into the forearm antecubital vein for 24 hours post-dosing to avoid multiple skin punctures. The cannula was kept patent by flushing with 0.5 ml of isotonic saline solution after each blood sample withdrawal. The pre-dose blood sample was collected within a period of 2 hours before dosing. Blood samples of 5 ml were collected in pre-labeled vacutainers containing K_3EDTA as an anticoagulant during each period. For Cilacar 10 mg, the blood samples were collected during the study at sampling hours at pre-dose (0.00) and then at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, and 24.00 hours post dosing. A total of 21 blood samples were obtained from each subject in each period and for Cilacar 20 mg, the blood samples were withdrawn at pre-dose (0.00) and then at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, and 24.00 hours post dosing. A total of 18 blood samples was obtained from each subject in each period. Blood samples were collected within 2 minutes of the scheduled sampling time. For 10 mg and 20 mg, separated plasma was divided into two aliquots and stored in suitably labeled Ria vials. Blood samples collected at each time point were centrifuged at 4500 rpm, below 5º C for 10 minutes to separate plasma. The plasma samples were transferred to a deep freezer and stored at -20ºC ± 05ºC till the analysis was completed. Cilnidipine is light - sensitive hence dosing activity was performed under sodium vapor lamp(s).

Safety Assessment

In each period, subjects were monitored for vital signs and physical wellbeing was asked at the time of check-in, pre-dose and at 1.00, 3.00, 5.00, 12.00, and 24.00 hours' post-dose; approximately (all vital measurements was done within ± 60 minutes of the sample collection time, except for pre-dose). Pre-dose vitals were measured within 2.00 hours prior to dosing. Clinical examination was performed at the time of check in, 24.00 hours (check-out) in both the periods.

Analytical Method

Plasma samples were analyzed to quantify the concentration of Cilnidipine using a chromatographic method. The bioanalytical method was validated at the analytical laboratory for sensitivity, specificity, linearity, accuracy and precision (repeatability and reproducibility), percent recovery and stability of samples (freeze-thaw stability, bench-top stability, auto sampler stability, short-term and long-term stability of stock solution and internal standard).

Statistical Analysis

Statistical data analysis was achieved using SAS®, Version 9.4. Descriptive statistics including arithmetic mean, geometric mean, standard deviation (±SD) and coefficient of variation (CV) were done. for the purpose of bioequivalence testing, analysis of variance (ANOVA) 90% confidence intervals and intra subject variability.

Pharmacokinetic Analysis

Plasma concentrations at each time point for each subject of Cilnidipine, the pharmacokinetic parameters were calculated. Primary Pharmacokinetic Parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and Secondary Pharmacokinetic Parameters: K_{el}, $t_{½}$, T_{max}, extrapolated AUC & AUC ratio.

Criteria for Evaluation

The 90% confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ was the basis for concluding the equivalence of test and reference product. If the point estimate of the ratio and the confidence intervals are entirely included within the range of 80.00% - 125.00% for log-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Cilnidipine, then the "test" product was considered bioequivalent to the "reference" product.

RESULT

Cilacar 10 mg

Table 1: Pharmacokinetic parameters (Mean ± SD) of Cilacar vs Atelec Tablet 10 mg

Parameters	Mean ± SD	
	Test (T)	Reference (R)
C_{max} (ng/mL)	13.60 ±10.274	12.56 ±4.628
AUC_{0-t} (ng*hour/mL)	72.51 ±31.046	71.45 ±19.556
AUC_{0-inf} (ng*hour/mL)	81.65 ± 35.009	80.27 ±21.487
T_{max} (hours)	3.04 ± 0.967	3.33 ± 0.940
$T_{1/2}$ (hours)	5.47 ± 2.542	5.16 ± 1.627
K_{el} (hours $^{-1}$)	0.16 ± 0.074	0.15 ± 0.050

Table 2: Pharmacokinetic parameter (% Ratio) of Cilacar vs Atelec Tablet 10 mg

Parameters	Geometric Mean		% Ratio	90 % Confidence Interval	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
C_{max}	11.94	11.90	100.31	82.61	121.80
AUC_{0-t}	68.31	69.38	98.46	88.35	109.72
AUC_{0-inf}	76.68	77.96	98.36	87.54	110.52

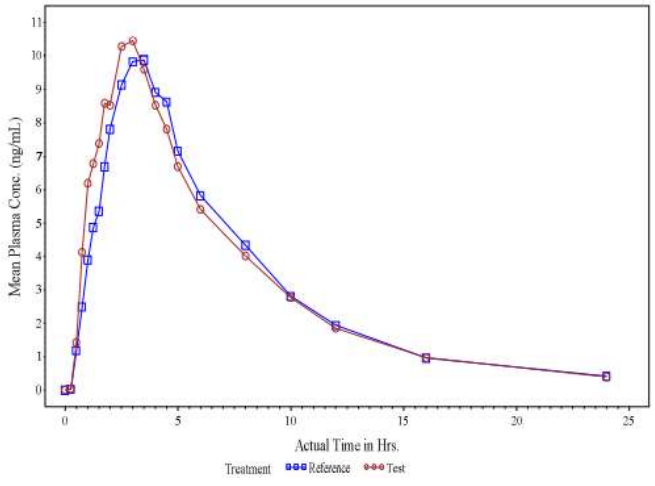

Figure 1: Mean plasma concentration vs time curve of Cilnidipine for Test (T) and Reference (R) product.

For Cilacar 10 mg, the Relative Bioavailability was 98.46% in comparison with that of Reference product.

Cilacar 20 mg

Table 3: Pharmacokinetic parameters (Mean ± SD) of Cilacar vs Atelec Tablet 20 mg

Parameters	Mean ± SD	
	Test (T)	Reference (R)
C_{max} (ng/mL)	19.6 ±9.96	19.42 ± 8.357
AUC_{0-t} (ng*hour/mL)	124.66 ±67.743	128.45 ± 72.848
AUC_{0-inf} (ng*hour/mL)	151.54 ± 88.369	153.72 ± 87.441
T_{max} (hours)	3.16 ± 1.526	2.70 ± 1.209
$T_{1/2}$ (hours)	0.13 ± 0.101	0.12 ± 0.066
K_{el} (hours $^{-1}$)	7.71 ± 4.413	7.68 ± 3.815

Table 4: Pharmacokinetic parameter (% Ratio) of Cilacar vs Atelec Tablet 20 mg

Parameters	Geometric Mean		% Ratio	90 % Confidence Interval	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
C_{max}	18.25	17.89	102.01	89.65	116.08
AUC_{0-t}	109.89	110.98	99.01	88.09	111.30
AUC_{0-inf}	131.46	132.87	98.94	88.35	110.79

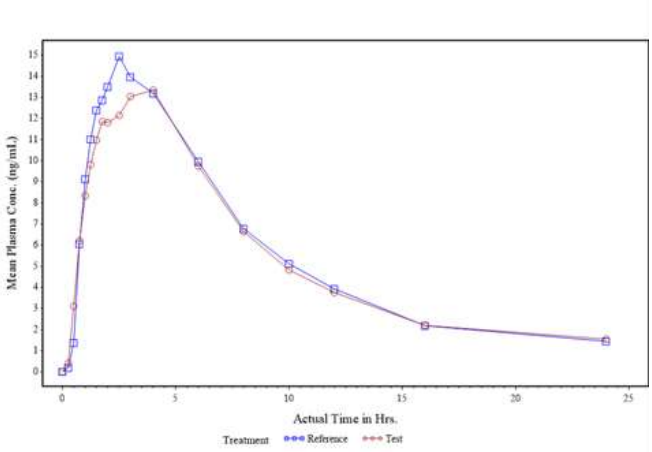

Figure 2: Mean plasma concentration vs time curve of Cilnidipine for Test (T) and Reference (R) Product.

For Cilacar 20 mg, the Relative Bioavailability was 99.01% in comparison with that of Reference product.

Dissolution Test

An *in vitro* dissolution study was also conducted to understand the dissolution profile of Cilacar 10 mg vs. other available generic brands in India., Data for one of the generics is presented here; Cilacar ["C"] (J. B. Chemicals & Pharmaceuticals Ltd.) vs. Generic [N]). Dissolution of both the products was analyzed in 2 types of buffers – Citro-phosphate buffer and Tween 80.

Table 5: Percentage drug release – *in vitro* dissolution profile.

Time in Minutes	Dissolution (Citro-Phosphate Buffer in 1%w/v SLS pH 6.8, 75 RPM, Paddle, 900 ml)		Dissolution (0.1% Tween 80 in water, 75 RPM, Paddle, 900 ml)	
	C (%)	N (%)	C (%)	N (%)
5	29	32	13	16
10	57	47	23	18
15	70	57	28	21
20	78	65	32	24
30	84	71	37	28
45	89	79	42	32
60	92	85	46	35
Dissolution of competitor brand [N] vs [C], Dissolution of Cilacar observed to be faster in 60 min				

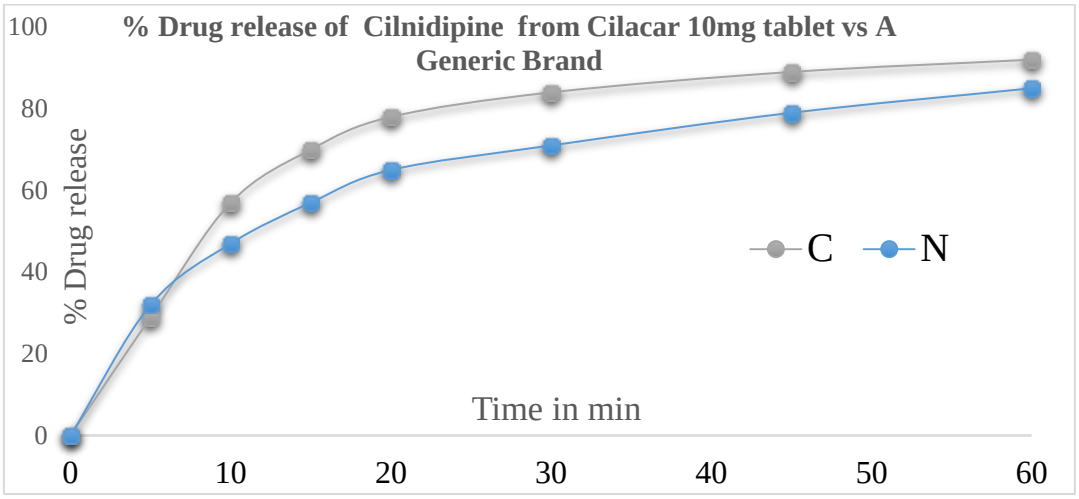

Figure 3: Dissolution (Citro-Phosphate Buffer in 1%w/v SLS pH 6.8, 75 RPM, Paddle,900 ml)

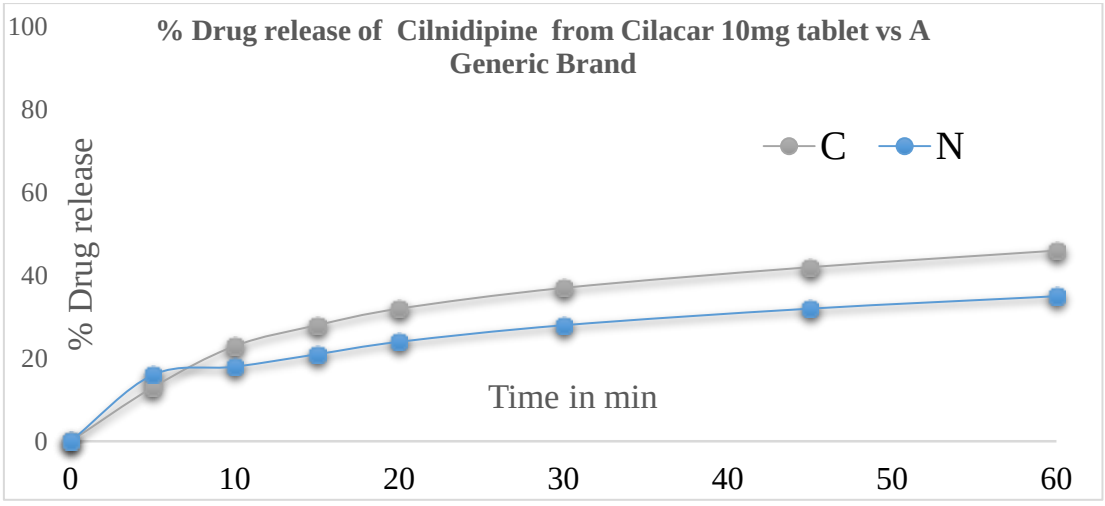

Figure 4: Dissolution (0.1% Tween 80 in water, 75 RPM, Paddle, 900 ml)

DISCUSSION

Cilnidipine has over the years been established as a reno-protective, cardio-protective, and neuro-protective CCB. As compared to other DHP-CCBs, Cilnidipine displays a better reno-protective profile, and hence has become a CCB of choice in the management of essential hypertension. Studies have demonstrated Cilnidipine to be effective for morning hypertension and white-coat hypertension as well, both of which are associated with high sympathetic activity. A study by Ramya et al concluded Cilnidipine to be safe and effective in reducing microalbuminuria and blood pressure in Indian mild-to-moderate hypertensive patients with type 2 diabetes mellitus. In a study conducted in 2920 hypertensive patients, treatment with Cilnidipine and angiotensin receptor blocker showed a significant reduction in heart rate, especially in those with a higher baseline heart rate (≥75 beats/min).[4]

Among the varied pleiotropic benefits that the molecule has to offer, apart from its anti-hypertensive efficacy, the cardioprotective effects of Cilnidipine are well depicted through the CANDLE trial and other clinical studies which have demonstrated that Cilnidipine improves left ventricular function. The molecule thus may be favorable for various types of chronic complications (renal and cardio-vascular) arising due to hypertension.[4] A recent Indian study comparing Cilnidipine to Amlodipine concluded that despite similar blood pressure reduction, Cilnidipine therapy causes no increase in the heart rate due to its N-type calcium channel blockade. A recent study by Napolean et al.,[10] concluded that Cilnidipine can be used as a first line antihypertensive drug with its efficacy is comparable to that of Amlodipine and a better safety profile than Amlodipine. A study by R. Shetty et al. in 27 patients of essential hypertension with amlodipine-induced ankle edema concluded that therapy with Cilnidipine resulted in complete resolution of Amlodipine-induced edema in all the cases without significant worsening of hypertension or tachycardia.

Various studies have concluded Cilnidipine to be a potent and long-acting CCB. Once daily administration of Cilnidipine (5 - 20 mg) for a duration of 1 - 3 weeks decreased the 24-hour average BP significantly without any change in the heart rate. It is postulated that Cilnidipine exhibits a high protein binding of 98% along with a high volume of distribution, which prolongs the duration of action of the molecule. A 2021 meta-analysis presented by Chakraborty R et al.[7] concluded that Cilnidipine significantly reduced systolic blood pressure, diastolic blood pressure, and pulse rate in hypertensive patients.

For therapeutic effectiveness and bio-availability, the dissolution profile of a drug is crucial. The oral bioavailability of a drug is determined by multiple properties like solubility, intestinal permeability, pre-systemic metabolism, one of which is drug dissolution rate. Frequently, the rate - limiting

step in drug absorption from the gastrointestinal tract is drug release and drug dissolution from the dosage form. The absorption of compounds such as Cilnidipine, when presented in the crystalline state to the gastrointestinal tract is typically dissolution rate-limited, and the drugs are typically BCS Class II or Class IV compounds.

In this study, we analyzed the dissolution pattern of the Indian innovator brand Cilacar® in comparison to the innovator – Atelec®. The above data concludes that the dissolution profile[9] of the Indian innovator brand Cilacar® was bio-equivalent to Atelec® for the rate and extent of absorption, as analyzed by the various pharmacokinetic parameters such as AUC ($_{0\text{-}t}$), AUC ($_{0\text{-}inf}$), and C_{max}. Cilacar® was the first brand of Cilnidipine which was approved in India, by the Drug Controlled General of India (DCGI) for the management of essential hypertension, and thus it is also treated as a Reference Listed Drug (RLD) for all Cilnidipine products manufactured in India[11]. The study also analyzed the dissolution profile with other available generic brands, from which we can affirm the RLD status in India.

CONCLUSION

Hypertension requires tight blood pressure control to reduce the risk for renal or cardiovascular disease. Cilnidipine is a DHP-CCB, that acts on the L and the N types of calcium channel of blood vessels by blocking incoming calcium and suppressing the contraction of blood vessels, thereby reducing blood pressure. This study was conducted with the objective to compare Cilacar (Cilnidipine) 10 and 20 mg tablet to Atelec and proved its bioequivalence and reference status in India. The NIDAT* technology in the brand Cilacar tablet, enhances the dissolution profile depicting faster and better dissolution, which is also evident from the comparative dissolution assay conducted with generics of Cilnidipine.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

BE study was a sponsored study from Unique Pharmaceuticals.

ABBREVIATIONS of Products

For Dissolution profile:

C- Cilacar (Unique pharmaceuticals Pvt. Ltd)

N- Nexovas (Macleod's Pharmaceuticals Ltd)

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